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Your reference	144425GB01
Patent application number *(The Patent Office will fill in this part)*	0326768.9 17 NOV 2003
Full name, address and postcode of the or of each applicant *(underline all surnames)*	BTG International Limited 10 Fleet Place Limeburner Lane London EC4M 7SB GB
Patents ADP number *(if you know it)*	7443872001
If the applicant is a corporate body, give the country/state of its incorporation	GB
Title of the invention	GENERATION OF THERAPEUTIC MICROFOAM
Name of your agent *(if you have one)*	Paul Simpson
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	BTG International Limited 10 Fleet Place Limeburner Lane London EC4M 7SB GB
Patents ADP number *(if you know it)*	

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Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	YES

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11. I/We request the grant of a patent on the basis of this application.

Signature [signature] Date 17/11/03

Paul Simpson

12. Name and daytime telephone number of person to contact in the United Kingdom **BAYLIS, Steve 020 7575 1583**

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GENERATION OF THERAPEUTIC MICROFOAM

The present invention relates to the generation of microfoam comprising a sclerosing material, particularly a sclerosing liquid, which is suitable for use in the treatment of various medical conditions involving blood vessels, particularly varicose veins and other disorders involving venous malformation.

Sclerosis of varicose veins is based on the injection into the veins of liquid sclerosant substances which, by *inter alia* causing a localised inflammatory reaction, favour the elimination of these abnormal veins. Until recently, sclerotherapy was a technique selected in cases of small and medium calibre varicose veins, those with diameters equal to or greater than 7 mm being treated by surgery.

An injectable microfoam suitable for therapeutic use, on larger veins in particular, has now been developed and is described in EP-A-0656203 and US 5676962, incorporated herein by reference. These describe a low-density microfoam produced with a sclerosing substance which, when injected into a vein, displaces blood and ensures that the sclerosing agent contacts the endothelium of the vessel in a known concentration and for a controllable time, achieving sclerosis of the entire segment occupied.

The preparation of such a microfoam may be carried out with a solution of any sclerosing substance, particularly polidocanol. The method of preparation is to use a small brush attached to a high-speed motor to whip a dilute aqueous solution of the preferred sclerosant to a firm mousse-like consistency in a period of 1–2 minutes under a gas atmosphere containing physiologically acceptable gas mixes. However, this known method requires extemporaneous production of microfoam by the physician, pharmacist or an assistant immediately prior to administration to the patient. Such procedure allows for variation of microfoam sclerosing agent depending upon the person preparing it; microfoam density, gas makeup, bubble size and foam stability all needing attention with respect to the condition being treated.

A solution to this problem is offered in WO 00/72821-A1 (BTG International Limited), incorporated herein by reference, which provides a method and a number of different devices that are capable of producing a uniform injectable microfoam. This microfoam is made with a relatively low concentration of a foamable sclerosing agent and a significant amount of a blood dispersible gas in sterile fashion without volatile liquid propellants or the need for the operator to directly be concerned in the control

of its parameters. This application also addresses the perception that large volumes of nitrogen should not unnecessarily be introduced into patients. This is particularly an issue where large vessels are being filled with foam, if air is used as the gas for producing the foam. A preferred form of gas described in WO 00/72821-A1 comprises 50% vol/vol or more oxygen, the remainder being carbon dioxide, or carbon dioxide, nitrogen and trace gases in the proportion found in atmospheric air. Preferably the sclerosing agent is a solution of polidocanol or sodium tetradecyl sulfate in an aqueous carrier, e.g. water, particularly in a saline.

In WO 02/41872-A1 (BTG International Limited), incorporated herein by reference, the sclerosant liquid and the oxygen-rich physiologically acceptable blood dispersible gas of WO 02/41872-A1 are stored in separate containers until immediately prior to use, when the blood-dispersible gas is introduced into the container holding the sclerosant liquid. The mixture of blood-dispersible gas and sclerosant liquid is then released, the components of the mixture interacting upon release of the mixture to form a sclerosing foam.

The device disclosed in WO 00/72821-A1 gives a good uniform injectable microfoam, irrespective of the gases used. Use of 100% CO_2 as the filling gas in the polidocanol canister is preferred, as CO_2 is very soluble in the bloodstream, but the present inventors have observed that increasing CO_2 percentage in the final gas mix may cause an undesirable decrease in microfoam stability, resulting in a shorter half separation time. In particular, the half-life of the microfoam can fall short of the figure of 2.5 minutes which is indicated in WO 00/72821-A1 as being preferable.

Accordingly the first aspect of the present invention provides a method for producing a microfoam suitable for use in scleropathy of blood vessels, particularly veins, characterized in that it comprises passing a mixture of a physiologically acceptable blood dispersible gas and an aqueous sclerosant liquid through one or more passages having at least one cross-sectional dimension of from 0.1 to 15 μm, the ratio of gas to liquid being controlled such that a microfoam is produced having a density of between 0.07 g/mL to 0.19 g/mL and a half-life of at least 2.5 minutes.

For the purpose of this application terms have the following definitions: Physiologically acceptable blood dispersible gas is a gas that is capable of being substantially completely dissolved in or absorbed by blood. A sclerosant liquid is a liquid that is capable of sclerosing blood vessels when injected into the vessel lumen.

Scleropathy or sclerotherapy relates to the treatment of blood vessels to eliminate them. An aerosol is a dispersion of liquid in gas. A major proportion of a gas is over 50% volume/volume. A minor proportion of a gas is under 50% volume/volume A minor amount of one liquid in another liquid is under 50% of the total volume. Atmospheric pressure and bar are 1000 mbar gauge. Half-life of a microfoam is the time taken for half the liquid in the microfoam to revert to unfoamed liquid phase.

Preferably the microfoam is such that 50% or more by number of its gas bubbles of 25 μm diameter and over are no more than 200 μm diameter.

Preferably the gas/liquid ratio in the mix is controlled such that the density of the microfoam is 0.09 g/mL to 0.16 g/mL, more preferably 0.11 g/mL to 0.14 g/mL.

Preferably the microfoam has a half-life of at least 3 minutes. The half-life may be as high as 1 or 2 hours or more, but is preferably less than 60 minutes, more preferably less than 15 minutes and most preferably less than 10 minutes.

Half-life is conveniently measured by filling vessel with a known volume and weight of foam and allowing liquid from this to drain into a graduated vessel, the amount drained in a given time allowing calculation of half-life i.e. of conversion of microfoam back into its component liquid and gas phases. This is preferably carried out at standard temperature and pressure, but in practice ambient clinic or laboratory conditions will suffice.

Preferably the mixture of gas and sclerosant liquid is in the form of an aerosol, a dispersion of bubbles in liquid or a macrofoam. By macrofoam is meant a foam that has gas bubbles that are measured in millimetres largest dimension, e.g. approximately 1 mm and over, and over such as can be produced by lightly agitating the two phases by shaking. Preferably the gas and liquid are in provided in the form of an aerosol where a source of pressurized gas and a means for mixing the two is provided to the point of use. It may be preferred that a macrofoam is first produced where the liquid and gas are brought together only at the point of use.

The ratio of gas to liquid used in the mixture is important in order to control the structure of the microfoam produced such that its stability is optimized for the procedure and the circumstances in which it is being carried out. For optimum foams it is preferred to mix 1 gram sclerosant liquid with from approximately 6.25 to 14.3 volumes (STP), more preferably 7 to 12 volumes (STP), of gas.

Preferably the physiologically acceptable blood dispersible gas comprises a major proportion of carbon dioxide and/or oxygen. Conveniently it may comprise a minor proportion of nitrogen or other physiologically acceptable gas. While a proportion of nitrogen may be present, as in air, the present invention provides for use of carbon dioxide and/or oxygen without presence of nitrogen.

In one preferred form the gas used is a mixture of carbon dioxide and other physiological gases, particularly containing 3% or more carbon dioxide, more preferably from 10 to 90% carbon dioxide, most preferably 30 to 50% carbon dioxide. The other components of this gas are preferably oxygen with a minor proportion only of nitrogen being preferred. Most preferably the other component is oxygen.

A further preferred form of gas comprises 50% vol/vol or more oxygen, the remainder being carbon dioxide, or carbon dioxide, nitrogen and trace gases in the proportion found in atmospheric air. One preferred gas is 60 to 90% vol/vol oxygen and 40 to 10% vol/vol carbon dioxide, more preferably 70 to 80% vol/vol oxygen and 30 to 20% vol/vol carbon dioxide. More preferred is 99% or more oxygen.

It is found that passing a stream of the sclerosant liquid and the gas under pressure through one or more passages of 0.1 μm to 15 μm as described provides a stable blood dispersible gas based sclerosant injectable microfoam that was previously thought to be only producible by supply of high amounts of energy using high speed brushes and blenders.

Preferably the sclerosing agent is a solution of polidocanol or sodium tetradecylsulfate in an aqueous carrier, e.g. water, particularly in a saline. More preferably the solution is from 0.5 to 5% v/v polidocanol, preferably in sterile water or a physiologically acceptable saline, e.g. in 0.5 to 1.5% v/v saline. Concentration of sclerosant in the solution will be advantageously increased for certain abnormalities such as Klippel–Trenaunay syndrome.

Polidocanol is a mixture of monolauryl ethers of macrogols of formula $C_{12}C_{25}(OCH_2CH_2)_nOH$ with an average value of n of 9. It will be realized that mixtures with other alkyl chains, oxyalkyl repeat units and/or average values of n might also be used, e.g. 7 to 11, but that 9 is most conveniently obtainable, e.g. from Kreussler, Germany, e.g. as Aethoxysklerol™, a dilute buffered solution of polidocanol.

Most preferably the concentration of sclerosant in the aqueous liquid is a 1–3% vol/vol solution, preferably of polidocanol, in water or saline, more preferably about 1% vol/vol. The water or saline also, in some cases at least, preferably contain 2–4% vol/vol physiologically acceptable alcohol, e.g. ethanol. Preferred saline is buffered. Preferred buffered saline is phosphate buffered saline. The pH of the buffer is preferably adjusted to be physiological, e.g. from pH 6.0 to pH 8.0, more preferably about pH 7.0.

The sclerosant may also contain additional components, such as stabilizing agents, e.g. foam stabilizing agents, e.g. such as glycerol. Further components may include alcohols such as ethanol.

The aerosol, dispersion or macrofoam is preferably produced by mixing the gas and liquid from respective flows under pressure. The mixing conveniently is carried out in a gas liquid interface element such as may be found in aerosol canisters. The interface device may however be very simple, such as a single chamber or passage of millimetre dimensions, i.e. from 0.5 to 20 mm diameter, preferably 1 to 15 mm diameter, into which separate inlets allow entry of gas and liquid. Conveniently the interface is of design which is commonly found in aerosol canisters but which is selected to allow the correct ratio of gas to liquid to allow formation of a foam of the presently defined density. Suitable inserts are available from Precision Valves (Peterborough UK) under the name Ecosol and are selected to produce the ratio specified by the method above.

However, the mixing of gas and liquid may also be brought about within a dip-tube leading from the sclerosant solution located in the bottom of a pressurized container where holes in the dip-tube allow gas to enter into a liquid stream entering from the bottom of the tube. In this case the holes may be of similar diameter to the Ecosol holes. Such holes may be conveniently produced by laser drilling of the dip-tube.

The one or more passages through which the aerosol or macrofoam so produced are passed to produce the stable microfoam preferably have diameter of from 4 μm to 22 μm, more preferably from 5 μm to 11 μm where simple passages are provided, such as provided by openings in a mesh or screen, e.g. of metal or plastics, placed perpendicular to the flow of gas/liquid mixture. The passage is conveniently of

circular or elliptical cross section, but is not necessarily so limited. A number of such meshes or screens may be employed along the direction of flow.

Most preferably the passages are provided as multiple openings in one or more elements placed across the flow. Preferably the elements are from 2 to 30 mm diameter, more preferably 6 to 15 mm diameter, face on to the flow, with 5 to 65% open area, e.g. 2% to 20% open area for woven meshes and 20% to 70% open area for microporous membranes. Openings in a porous material, such as provided in a perforated body, preferably provide several hundreds or more of such passages, more preferably tens or hundred of thousands of such passages, e.g. 10,000 to 500,000, presented to the gas liquid mixture as it flows. Such material may be a perforated sheet or membrane, a mesh, screen or sinter. Still more preferably a number of sets of porous material are provided arranged sequentially such that the gas and liquid pass through the passages of each set. This leads to production of a more uniform foam.

Where several elements are used in series these are preferably spaced 1 to 5 mm apart, more preferably 2 to 4 mm apart e.g. 3 to 3.5 mm apart.

For some embodiments of the present invention it is found that the passage may take the form of a gap between fibres in a fibrous sheet placed across the path of the gas/liquid flow, and the dimension described in not necessarily the largest diameter, but is the width of the gap through which the gas/liquid aerosol or macrofoam must flow.

Alternatively the method provides for passing the mixture of gas and liquid through the same set of passages, e.g. as provided by one or more such porous bodies, a number of times, e.g. from 2 to 2,000, more preferably 4 to 200 times, or as many times as conveniently results in a microfoam of the required bubble size distribution set out above. It will be realized that the more times the microfoam passes through the meshes, the more uniform it becomes.

The pressure of the gas used as it is passed through the passages will depend upon the nature of the mechanism used to produce the foam. Where the gas is contained in a pressurized chamber, such as in an aerosol canister, in contact with the liquid, suitable pressures are typically in the range 0.01 to 9 bar over atmosphere. For use of meshes, e.g. 1 to 8 meshes arranged in series, having apertures of 10–20 μm diameter, 0.1 to 5 atmospheres over bar will, *inter alia*, be suitable. For use of 3–5 meshes of 20 μm aperture it is found that 1.5–1.7 bar over atmospheric is sufficient to

produce a good foam. For a 0.1 μm pore size membrane, a pressure of 5 bar or more over atmospheric pressure is preferred.

In one preferred form of the invention the passages are in the form of a membrane, e.g. of polymer such as polytetrafluoroethylene, wherein the membrane is formed of randomly connected fibres and has a rated effective pore size which may be many times smaller than its apparent pore size. A particularly suitable form of this is a biaxially oriented PTFE film provided by Tetratec™ USA under the trademark Tetratex™, standard ratings being 0.1 to 10 μm porosity. Preferred pore sizes for the present method and devices are 3 to 7 μm. This material may be laminated with a porous backing material to give it strength and has the advantage that one pass through may be sufficient to produce a foam that meets the use requirements set out above with regard to stability. However, it will evident to those skilled in the art that use of more than one such membrane in series will give a still more uniform foam for given set of conditions.

It is believed that the combination of provision of a stream of solution and gas under pressure through an aerosol valve and then flow through the passages, e.g. pores in a mesh, screen, membrane or sinter provides energy sufficient to produce a stable aqueous liquid soluble gas, e.g. carbon dioxide and/or oxygen, based sclerosant microfoam that was previously thought to be only producible by supply of high amounts of energy using high speed brushes and blenders as described in the prior art.

A most preferred method of the invention provides a housing in which is situated a pressurisable chamber. For sterile supply purposes this will at least partly filled with a sterile and pyrogen free solution of the sclerosing agent in a physiologically acceptable aqueous solvent but otherwise may be charged with such at the point of use. This convenient method provides a pathway by which the solution may pass from the pressurisable chamber to exterior of the housing through an outlet and more preferably a mechanism by which the pathway from the chamber to the exterior can be opened or closed such that, when the container is pressurized, fluid will be forced along the pathway and through one or more outlet orifices.

The method is particularly characterized in that the housing incorporates one or more of (a) a pressurized source of the physiologically acceptable gas that is readily dispersible in blood, and (b) an inlet for the admission of a source of said gas; the gas being contacted with the solution on activation of the mechanism.

The gas and solution are caused to pass along the pathway to the exterior of the housing through the one or more, preferably multiple, passages of defined dimension above, through which the solution and gas must pass to reach the exterior, whereby on contact with, e.g. flow through, the passages the solution and gas form a the microfoam.

Preferably the gas and liquid pass through a gas liquid interface mechanism, typically being a junction between a passage and one or more adjoining passages, and are converted to an aerosol, dispersion of bubbles or macrofoam before passing through the passages, but as explained they may be converted first to a macrofoam, e.g. by shaking of the device, e.g., by hand, or mechanical shaking device.

In a second aspect of the present invention there is provided a device for producing a microfoam suitable for use in scleropathy of blood vessels, particularly veins, comprising a housing in which is situated a pressurisable chamber containing a solution of the sclerosing agent in a physiologically acceptable solvent referred to in the first aspect; a pathway with one or more outlet orifices by which the solution may pass from the pressurisable chamber to exterior of the device through said one or more outlet orifices and a mechanism by which the pathway from the chamber to the exterior can be opened or closed such that, when the container is pressurized and the pathway is open, fluid will be forced along the pathway and through the one or more outlet orifices

said housing incorporating one or more of (a) a pressurized source of physiologically acceptable gas that is dispersible in blood and (b) an inlet for the admission of said gas; the gas being in contacted with the solution on activation of the mechanism such as to produce a gas solution mixture

said pathway to the exterior of the housing including one or more elements defining one or more passages of cross sectional dimension, preferably diameter, 0.1 μm to 15 μm, through which the solution and gas mixture is passed to reach the exterior of the device, said passing of said mixture through the passages forming a microfoam of from 0.07 to 0.19 g/mL density and of half-life at least 2 minutes.

Preferably the microfoam has 50% or more by number of its gas bubbles of 25 μm diameter and over of no more than 200 μm diameter.

More preferably the microfoam is from 0.09 to 0.16 g/mL density and most preferably of 0.11 g/mL to 0.14 g/mL.

Preferably the microfoam has a half-life of at least 2.5 minutes, more preferably at least 3 minutes.

Preferably the apparatus includes a chamber, e.g. such as in a sealed canister, charged with the blood dispersible gas and the sclerosant liquid, e.g. in a single chamber, the device pathway including a dip tube with an inlet opening under the level of the liquid in this chamber when the device is positioned upright. Preferably the dip-tube has an outlet opening at a gas liquid interface junction where the gas, which resides in the chamber above the liquid, has access to the pathway to the device outlet. The pathway is opened or closed by a valve element which is depressed or tilted to open up a pathway to the exterior of the device, whereby the liquid rises up the dip tube under gas pressure and is mixed in the interface junction with that gas to produce an aerosol, dispersion of bubbles in liquid or macrofoam.

Either inside the pressurisable chamber disposed in the pathway to the valve, or on the downstream side of the valve, is provided an element having the one or more passages described in the first aspect mounted such that the gas liquid mixture, i.e. dispersion of bubbles in liquid, aerosol or macrofoam,, passes through the passage or passages and is caused to foam. This element may conveniently be located in a cap on the canister in between the valve mounting and an outlet nozzle. Conveniently depression of the cap operates the valve. Alternatively the element is within the canister mounted above the gas liquid interface.

In an alternate embodiment of this device the gas liquid interface may comprise holes in the dip tube above the level of the liquid in the canister inner chamber.

The gas pressure employed will be dependent upon materials being used and their configuration, but conveniently will be 0.01 to 9 bar over atmospheric, more preferably 0.1–3 bar over atmospheric, and still more preferably 1.5–1.7 bar over atmospheric pressure.

A preferred device of this aspect of the invention is of the 'bag-on-valve' type. Such device includes a flexible gas and liquid tight container, forming a second inner chamber within the pressurisable chamber, which is sealed around the dip-tube and filled with the liquid. More preferably the dip-tube has a one-way valve located at a position between its end located in the sclerosant liquid and the gas liquid interface junction, which when the passage to the exterior is closed, remains closed such as to separate the liquid from the physiologically acceptable blood dispersible gas around it

in the chamber. On opening the pathway to the exterior, the one way valve also opens and releases liquid up the dip-tube to the gas liquid interface where an aerosol is produced which is in turn then passed through the passages to be converted to microfoam. A suitable one-way valve is a duck-bill type valve, e.g. such as available from Vernay Labs Inc, Yellow Springs, Ohio, USA. Suitable bag-on-valve can constructions are available from Coster Aerosols, Stevenage, UK and comprise an aluminium foil/plastics laminate.

Conveniently the one way valve is located at the top of the dip-tube between that and the gas liquid interface junction, i.e. an Ecosol device. This allows filling of the bag before application of the one way valve, followed by sterilization of the contents, whether in the canister or otherwise.

Such a preferred device has several potential advantages. Where oxygen is the gas, this is kept separate from the liquid before use and thus reduces possibility of oxygen radicals reacting with organic components in the liquid, e.g. during sterilization processes such as irradiation. Where carbon dioxide is the gas, storage can lead to high volumes of gas dissolving in the liquid, which on release to the atmosphere or lower pressure, could out-gas and start to destroy the microfoam too quickly. Such separation also prevents the deposition of solidified sclerosing agent components in the dimension sensitive orifices of the device in an unused can in storage or transit, particularly should that be oriented other than upright.

It is preferred that the gas liquid interface is provided as a defined orifice size device such as the Ecosol device provided by Precision Valve Peterborough UK. For a device where the passages of defined dimension are outside of the pressurized chamber, i.e. mounted on the valve stem, the ratio of area of the gas holes to the liquid holes should be of the order of 3 to 5, preferably about 4. Where the passages are inside the pressurized chamber this is preferably higher.

A third aspect of the invention provides a device for producing a microfoam suitable for use in sclerotherapy of blood vessels, particularly veins, comprising a housing in which is situated a pressurisable chamber, at least part filled or fillable with a solution of a sclerosing agent in a physiologically acceptable solvent and/or a physiologically acceptable blood dispersible gas; a pathway by which the contents of the chamber may be passed to exterior of the housing through one or more outlet orifices and a mechanism by which the chamber can be pressurized such that its

contents pass to the exterior along the pathway and through one or more outlet orifices

said pathway to the exterior of the housing or the chamber including one or more elements defining one or more passages of cross sectional dimension, preferably diameter, 0.1 μm to 15 μm through which the contents of the chamber may be passed, whereby on passing through the passages the solution and gas form a microfoam of from 0.07 to 0.19 g/mL density and having a half-life of at least 2 minutes.

Preferably the microfoam is such that 50% or more by number of its gas bubbles of 25 μm or more diameter are of no more than 200 μm diameter.

Preferably the microfoam is of density 0.09 to 0.16 g/mL and more preferably of 0.11 g/mL to 0.14 g/mL. The preferred limits on bubble size are also as for the first and second aspects.

Preferably the microfoam has a half-life of at least 2.5 minutes, more preferably at least 3 minutes

The elements defining the passages in the pathway or chamber may be static or may be moveable by manipulation of the device from outside of its interior chamber.

Preferably the housing is a container defining a chamber in which is situated the solution and gas under pressure and the pathway is a conduit leading from the chamber in the interior of the container to a valve closing an opening in the container wall.

Preferred forms of the one or more elements defining the multiple passages for use in the device of the present invention are meshes, screens or sinters. Thus one or more meshes or perforated screens or sinters will be provided, with some preferred forms employing a series of such elements arranged in parallel with their major surfaces perpendicular to the path of solution/gas expulsion.

It is preferred that all elements of any of the devices according to the invention having a critical dimension are made of a material that does not change dimension when exposed to aqueous material. Thus elements with such function such as the air liquid interface and the element defining the passages of 0.1 μm–15 μm dimension preferably should not be of a water swellable material such as Nylon 66 where they are likely to be exposed to the solution for more than a few minutes.

Where such exposure is likely these parts are more preferably being fashioned from a polyolefin such as polypropylene or polyethylene.

Preferably the canister is sized such that it contains sufficient gas and solution to form up to 500 mL of microfoam, more preferably from 1 mL up to 200 mL and most preferably from 10 to 60 mL of microfoam. Particularly the amount of gas under pressure in such canisters should be sufficient to produce enough foam to treat, i.e. fill, at least one varicosed human saphenous vein. Thus preferred canisters of the invention may be smaller than those currently used for supply of domestic used mousse type foams. The most preferred canister device is disposable after use, or cannot be reused once opened such as to avoid problems of maintaining sterility.

It may be preferred to incorporate a device which maintains gas pressure in the canister as foam is expelled. Suitable devices are such as described under trademarked devices PECAP and Atmosol. However, where a significant headspace or pressure of gas is provided this will not be necessary.

A fourth aspect of the present invention provides improved microfoams for use in the elimination of blood vessels and vascular malformations that are made available by the method and devices of the invention, comprising a physiologically acceptable gas that is readily dispersible in blood together with an aqueous sclerosant liquid wherein in that the microfoam has a density of from 0.07 to 0.19 g/cm and is capable of being passed down a 21 gauge needle without reverting back to gas and liquid by more than 10%, based on liquid content reverting back to unfoamed liquid phase. Preferably the microfoam has a half-life as measured by drainage through a funnel of 2 cm neck diameter and drainage path 10 cm of at least 2.5 minutes and most preferably 3 minutes. This may be carried out at ambient temperature or STP. Most conveniently the funnel is pre-equilibrated in a water bath to ensure a temperature of 25°C before drying and application of foam. Placing of a microfoam filled syringe upside down, without its plunger, above the funnel leading into a graduated receptacle allows convenient measurement of this parameter.

Preferably the microfoam, on passage through said needle, does not revert back to unfoamed liquid by more than 5% based on liquid content, still more preferably by no more than 2%.

Preferably the microfoam is capable of being passed down a needle while retaining at least 50% by number of its gas bubbles of at least 25 μm diameter at no

more than 200 μm diameter. This is conveniently measured under ambient conditions, more preferably at STP.

Preferably the gas includes less than 40% v/v nitrogen. Preferably the density of the microfoam is from 0.09 to 0.16 g/mL, more preferably 0.11 g/mL to 0.14 g/mL.

Preferably the foam density, which is a measure of liquid/gas ratio, is from 0.13 to 0.14 g/cm and the half-life is at least 2.5 minutes. The foam more preferably does not move outside of its parameters of bubble size set out above in such time.

Preferably the gas consists of at least 50% oxygen or carbon dioxide, more preferably 75% or more oxygen or carbon dioxide and most preferably at least 99% oxygen or carbon dioxide, e.g. substantially 100% oxygen or carbon dioxide. Preferably the oxygen or carbon dioxide is medical grade.

Preferably the sclerosant is aqueous polidocanol or sodium tetradecyl sulfate.

When the sclerosant is aqueous polidocanol the concentration of polidocanol is from 0.5 to 4% vol/vol in the liquid, preferably being 1 to 3% vol/vol polidocanol and most preferably being 2% vol/vol in the liquid.

Advantageously the sclerosant is made up in water, but more advantageously is made up in a saline solution, particularly 10 to 70 mM phosphate buffered saline, e.g. 50 mM phosphate buffered saline, and preferably of pH 6 to pH 8.0 e.g. about pH 7.0. Advantageously the aqueous solution contains a minor amount of an alcohol, preferably 96% ethanol, e.g. at between 2 and 6% vol/vol, more preferably at about 4% vol/vol of 96% ethanol. Although this can reduce foam stability, it serves to solubilize the other elements

Addition of glycerol to the aforesaid sclerosant imparts a longer half-life to the resultant foam. However, glycerol also produces a tendency for the meshes to block up when using a mesh device as described above, so should be used carefully where the device it is produced from may be used multiple times or the bag-on-valve concept is used.

The invention also provides:

- a method of treating a patient in need of sclerotherapy of a blood vessel comprising administering a microfoam as described above to that blood vessel;

- use of a microfoam described above for the manufacture of a medicament for sclerotherapy; and
- a microfoam as described above for use in therapy.

The present invention will now be described further by way of illustration only by reference to the following Figures and Examples. Further embodiments falling within the scope of the invention will occur to those skilled in the art in the light of these.

FIGURES

Figure 1 shows a cross-sectional view of a pre-pressurised container for the generation of therapeutic microfoam according to the invention, as disclosed in WO 00/72821-A1 and further described in Example 1 below.

Figure 2 shows a shows a cross-sectional view of a device comprising a container provided with engaging means and a mesh stack shuttle according to the invention, as disclosed in WO 02/41872-A1 and further described in Example 2 below.

Figure 3 shows a graph to compare the results from the four bi-can conditions tested in Example 3 below, showing the effect of gas mix, gas pressure and shuttle mesh on microfoam density and half-life. Control 1 uses a 75% CO_2/25% N_2 gas mixture in a 0.5 bar canister with a 5 μm mesh; Test 1 uses the same gas mixture with a 5 μm mesh; Control 2 uses 100% CO_2 in a 1.2 bar canister with the 20 μm mesh; Test 2 uses the same gas with a 5 μm mesh.

Figure 4 shows a graph of the average number of bubbles by diameter from the four bi-can conditions tested in Example 3.

Figure 5 shows a graph of the proportion of bubbles by diameter from the four bi-can conditions tested in Example 3.

Figure 6 shows a graph of the average volume of bubbles by diameter from the four bi-can conditions tested in Example 3.

Figure 7 shows a graph of the proportion of bubbles by diameter from the four bi-can conditions tested in Example 3.

Figure 8 shows a graph to compare the results from the four bi-can conditions tested in Example 4 below, showing the effect of shuttle mesh size on half-separation time and density.

EXAMPLES

Example 1—pre-pressurised container

A typical apparatus for the generation of therapeutic microfoam according to the invention, as disclosed in WO 00/72821-A1, is shown in Figure 1.

The canister has an aluminium wall (1), the inside surface of which is coated with an epoxy resin. The bottom of the canister (2) is domed inward. The canister inner chamber (4) is pre-purged with 100% oxygen for 1 minute, containing 15 ml of a 1% vol/vol polidocanol / 20 mmol phosphate buffered saline solution / 4% ethanol, then filled with the required gas mixture.

A standard 1 inch diameter Ecosol™ aerosol valve (5) (Precision Valve, Peterborough, UK) is crimped into the top of the canister after sterile part filling with the solution and may be activated by depressing an actuator cap (6) to release content via an outlet nozzle (13) sized to engage a Luer fitting of a syringe or multi-way connector (not shown). A further connector (7) locates on the bottom of the standard valve and mounts four Nylon 66 meshes held in high density polyethylene (HDPE) rings (8), all within an open-ended polypropylene casing. These meshes have diameter of 6 mm and have a 14% open area made up of 20 μm pores, with the meshes spaced 3.5 mm apart.

A further connector (9) locates on the bottom of the connector holding the meshes and receives a housing (10) which mounts the dip tube (12) and includes gas receiving holes (11a, 11b) which admit gas from chamber (4) into the flow of liquid which rises up the dip-tube on operation of the actuator (6). These are conveniently defined by an Ecosol™ device provided by Precision Valve, Peterborough, UK, provided with an insert. Holes (11a, 11b) have cross-sectional area such that the sum total ratio of this to the cross-sectional area of the liquid control orifice at the base of the valve housing (at the top of the dip-tube) is controlled to provide the required gas/liquid ratio.

Example 2—container with engaging means and mesh stack shuttle

A device comprising a container provided with engaging means and a mesh stack shuttle according to the invention, as disclosed in WO 02/41872-A1, is shown in Figure 2. The device comprises a low pressure container (1) for an aqueous sclerosant liquid and an unreactive gas atmosphere, a container (2) for a

physiologically acceptable blood-dispersible gas and an engaging means comprising a connector (3).

The container (2) for a physiologically acceptable blood-dispersible gas is charged at 5.8 bar absolute pressure with the required gas mixture, whereas the container (1) is charged with an inert gas. Container (2) is used to pressurise container (1) at the point of use to approx 3.5 bar absolute and is then discarded, just before the microfoam is required. The two containers will thus be referred to hereinafter as the PD [polidocanol] can (1) and the O_2 can (2), and the term "bi-can" will be used to refer to the concept of two containers.

Each of the cans (1, 2) is provided with a snap-fit mounting (4, 5). These may be made as identical mouldings. The snap-fit parts (4, 5) engage the crimped-on mounting cup (6, 7) of each can (1, 2) with high frictional force. The connector is made in two halves (8, 9), and the high frictional force allows the user to grip the two connected cans (1, 2) and rotate the connector halves (8, 9) relative to each other without slippage between connector (3) and cans. Each of these can mountings (6, 7) has snap-fit holes (10, 11) for engaging mating prongs (12, 13) which are on the appropriate surfaces of the two halves (8, 9) of the connector.

The connector (3) is an assembly comprising a number of injection mouldings. The two halves (8, 9) of the connector are in the form of cam track sleeves which fit together as two concentric tubes. These tubes are linked by proud pins (14) on one half that engage sunken cam tracks (15) on the other half. The cam tracks have three detented stop positions. The first of these detents is the stop position for storage. An extra security on this detent is given by placing a removable collar (16) in a gap between the end of one sleeve and the other. Until this collar (16) is removed it is not possible to rotate the sleeves past the first detent position. This ensures against accidental actuation of the connector.

The cam track sleeves (8, 9) are injection moulded from ABS as separate items, and are later assembled so that they engage one another on the first stop of the detented cam track. The assembled sleeves are snap-fitted as a unit onto the O_2 can (2) mounting plate (5) via four locating prongs. The security collar is added at this point to make an O_2 can subassembly.

The connector (3) includes in its interior a series of foaming elements comprising a mesh stack shuttle (17) on the connector half (8) adjacent to the PD can (1). The mesh stack shuttle (17) is comprised of four injection moulded disk filters

with mesh hole size of 20 μm and an open area of approx. 14%, and two end fittings, suitable for leak-free connection to the two canisters. These elements are pre-assembled and used as an insert in a further injection moulding operation that encases them in an overmoulding (18) that provides a gas-tight seal around the meshes, and defines the outer surfaces of the mesh stack shuttle. The end fittings of the stack (17) are designed to give gas-tight face and/or rim seals against the stem valves (19, 20) of the two cans (1, 2) to ensure sterility of gas transfer between the two cans.

The mesh stack shuttle (17) is assembled onto the PD can valve (19) by push-fitting the components together in a aseptic environment.

The PD can (1) and attached shuttle (17) are offered up to the connector (3) and the attached O_2 can (2), and a sliding fit made to allow snap-fitting of the four locating prongs (12) on the PD can side of the connector (3) into the mating holes (10) in the mounting plate (4) on the PD can (1). This completes the assembly of the system. In this state, there is around 2 mm of clearance between the stem valve (20) of the O_2 can (2) and the point at which it will form a seal against a female Luer outlet from the stack.

When the security collar (16) is removed, it is possible to grasp the two cans (1, 2) and rotate one half of the connector (3) against the other half to engage and open the O_2 can valve (20).

As the rotation of the connector (3) continues to its second detent position, the PD can valve (19) opens fully. The gas flow from the O_2 can (2) is restricted by a small outlet hole (21) in the stem valve (20). It takes about 45 seconds at the second detent position for the gas pressure to (almost) equilibrate between the two cans to a level of 3.45 bar ± 0.15 bar.

After the 45 second wait at the second detent position, the connector (3) is rotated further to the third detent position by the user. At this position, the two cans (1, 2) can be separated, leaving the PD can (1) with half (8) of the connector and the shuttle assembly (17) captive between the connector and the PD can. The O_2 can (2) is discarded at this point.

A standard 1 inch diameter aerosol valve (19) (Precision Valve, Peterborough, UK) is crimped into the top of the PD can (1) before or after sterile filling with the solution and may be activated by depressing the mesh stack shuttle (17), which functions as an aerosol valve actuator mechanism, to release the contents via an outlet

nozzle (22) sized to engage a Luer fitting of a syringe or multi-way connector (not shown).

Example 3—Study to assess the effect on physical properties of micro-foam from changes to the mesh material in the mesh stack

This study outlines the effect on microfoam properties of changing the shuttle mesh pore size in a device according to Figure 2 from 20 microns to 5 microns, in combination with changes to the gas pressure and gas composition in the canister.

Two different gas compositions were used. In one, the canister containing the 1% polidocanol solution and a 75%/25% atmosphere of CO_2/N_2 is evacuated to 0.5 bar absolute pressure, whilst the other canister is pressurised to 5.9 bar absolute with oxygen. In the other, the canister containing the 1% polidocanol solution is pressurised to 1.2 ± 0.1 bar absolute with 100% CO_2, whilst the other canister is pressurised to 5.8 ± 0.1 bar absolute with oxygen.

The objective of the study is to examine and compare results obtained using 5 micron and 20 micron shuttle meshes, for PD canister pressures of 0.5 bar absolute with the current gas atmosphere and for 1.2 bar absolute PD canister pressures with a 100% CO_2 as the filling gas.

Materials and Methods

All sample preparation was performed in a laminar flow booth keeping exposure times to atmosphere to a minimum.

Shuttle units containing a stack of 4 nylon 6/6 woven meshes of 6 mm diameter in a class 100K cleanroom moulding facility were used. They differ in the following aspects shown in Table 1 below.

Table 1. Physical characteristics of the 20 μm and 5 μm meshes compared

Mesh Type	Thickness (μm)	Pore size (μm)	Open Area (% area of pores)	Thread diameter (μm)
5 μm	100	5	1	37
20 μm	55	20	14	34

Bioreliance Ltd, Stirling, Scotland, U.K., made the 1% polidocanol solution for the study under controlled conditions to the formula in Table 2.

Table 2. Composition of the 1% polidocanol solution

Material	Quantities	
	% $^{w}/_{w}$	per 1000 g
Polidocanol	1.000	10.00 g
Ethanol 96% EP	4.200	42.00 g
Disodium Hydrogen Phosphate Dihydrate. EP	0.240	2.40 g
Potassium Di-hydrogen Phosphate. EP	0.085	0.85 g
0.1 M Sodium Hydroxide Solution [used for adjustment of pH: 7.2–7.5]	q.s.	q.s.
0.1 M Hydrochloric Acid	q.s.	q.s.
Water for injection. EP [used to adjust to final weight]	approx. 94.475 q.s. to 100.00%	approx. 944.75g q.s. to 1000.00 g
TOTAL:	100.00%	1000.00 g

The polidocanol solution was sterile filtered using a 0.2-micron filter before filling into clean glass screw top bottles.

Bi-can assemblies were prepared for testing to the specifications of gas mix and pressure in the polidocanol canister detailed in Table 3.

Table 3. Summary of PD canister preparation for each treatment group

Canister Label	Sample Type	Gas Composition	Gas Pressure (bar absolute)	Mesh Pore Size (μm)
C	Control 1	75% CO_2/25% N_2	0.5	20
D	Test 1	75% CO_2/25% N_2	0.5	5
A	Control 2	100% CO_2	1.2	20
B	Test 2	100% CO_2	1.2	5

The order of testing of the experimental series was important, in that changes in ambient laboratory temperature affect the half separation time results. Experiments progressed cyclically through the sample types rather than test all of one sample type, followed by all of another sample type. This minimised the effect of any drift in laboratory temperature throughout the experiments. The laboratory temperature was maintained as close to 20 °C as possible.

It was also essential that the temperature of the half separation time apparatus be allowed to fully equilibrate to ambient room temperature following cleaning and drying steps between successive experimental measurements.

Summary of Tests

The tests and specifications performed on the bi-can units in this study are summarised in Table 4.

Table 4. Summary of tests and specifications

	TEST	SPECIFICATION
1	Appearance of Device	No corrosion of canisters or valves. Free from signs of leakage and external damage
2	Gas Pressure Polidocanol Canister Oxygen Canister	1.10 to 1.30 bar absolute for Type 2 samples 0.4 to 0.6 bar absolute for Type 1 samples 4.90 to 5.9 bar absolute
3.	Appearance of Micro-foam	Upon actuation, a white microfoam is produced. After the foam has settled, a clear and colourless liquid is observed.
4.	pH of Solution (collapsed microfoam)	6.6 to 7.5
5	Microfoam density	0.10 to 0.16 g/ml.
6	Microfoam Half Separation Time	150 to 240 seconds
7	Bubble Size (Diameter Distribution) < 30µm 30 µm to 280 µm 281 µm to 500 µm > 500µm	 ≤ 20.0% ≥ 75.0% ≤ 5.0% None
8	Particulates (Visible) and Sub-Visible)	Complies with Ph. Eur.
9	Particulates (Sub-Visible)	The collapsed microfoam contains not more than 1000 particles per ml ≥ 10 µm and not more than 100 particles ≥ 25 µm per ml.
10	Polidocanol identification by GC method	GC pattern and retention times to be equivalent to reference preparation
11	Polidocanol Assay	0.90 to 1.10% w/w
12	Related Substances	No single identified impurity >0.20% area. No single unidentified impurity >0.10% area. Total impurities ≤ 4.0% area

Results

Results of the tests described in Table 4 on bi-cans prepared as described in Table 3 are summarised in the following sections.

Appearance of device and foam

In all cases the appearance of the devices conformed to specification in that the device showed no corrosion of canisters or valves and were free from signs of leakage and external damage. Upon actuation of the charged PD canister a white microfoam was produced. After the foam had settled, a clear and colourless liquid was observed.

Density, half separation time and pH

Microfoam from all devices conformed to density and half separation time specification. However, one unexpectedly low result was obtained (C1 canister 1) but an additional two devices were tested which behaved as expected. In spite of the low result, the average conformed to specification. In general, microfoam generated via the 5 μm shuttles had longer half separation times. Results are summarised in Table 5 and are also shown graphically in Figure 3.

The average pH of the microfoam generated conformed to specification. However, microfoam produced from the 100% CO_2 canister were close to the lower limit of detection of the specification and in one instance (C2 canister 4) it was just below specification. Results summarised in Table 5.

The gas pressure in the oxygen cans and the polidocanol cans conformed to specification in all cases. In one instance (C1 canister 6) a slightly lower oxygen canister pressure than expected was recorded. Results are summarised here in Table 5.

Table 5. Table summarising the microfoam density, half separation time, pH and canister gas pressures

Test Condition	density (g/cm^3)	half life (sec)	pH	Gas pressure (bars abs) Oxygen	PD
Specification	**0.10-0.16**	**150-240**	**6.6-7.5**	**4.9-5.9**	**0.4-0.6**
100% CO_2, 1.2 Bar, 20 µm mesh					
Canister A1	0.12	164	6.7	5.6	1.1
Canister A2	0.13	150	6.7	5.5	1.1
Canister A3	0.13	153	6.6	5.8	1.1
Canister A4	0.15	154	6.5	5.5	1.1
Canister A5	0.13	154	6.7	5.6	1.1
Canister A6	0.15	154	6.5	5.6	1.1
Average	**0.13**	**155**	**6.6**	**5.6**	**1.1**
100% CO_2, 1.2 Bar, 5 µm mesh					
Canister B1	0.12	182	6.6	5.4	1.1
Canister B2	0.12	169	6.7	5.6	1.1
Canister B3	0.14	162	6.6	5.4	1.1
Canister B4	0.1	173	6.7	5.7	1.1
Canister B5	0.12	168	6.6	5.6	1.1
Canister B6	0.15	161	6.5	5.4	1.1
Average	**0.13**	**169**	**6.6**	**5.5**	**1.1**
75% CO_2/25% N_2, 0.5 Bar, 20 µm mesh					
Canister C1	0.14	157#	6.9	5.4	0.6
Canister C2	0.15	182	6.9	5.5	0.6
Canister C3	0.13	193	6.9	5.4	0.6
Canister C4	0.15	183	6.9	5.7	0.6
Canister C5	0.15	192	6.8	5.6	0.5
Canister C6	0.15	191	6.9	5.0	0.6
Canister C11	0.14	189	7.0	5.7	0.6
Canister C12	0.13	179	7.0	5.4	0.6
Average	**0.14**	**183**	**6.9**	**5.5**	**0.6**
75% CO_2/25% N_2, 0.5 Bar, 5 µm mesh					
Canister D1	0.15	203	6.9	5.4	0.6
Canister D2	0.12	209	7.0	5.6	0.6
Canister D3	0.16	198	6.8	5.6	0.6
Canister D4	0.12	205	6.9	5.7	0.6
Canister D5	0.12	208	6.9	5.4	0.6
Canister D6	0.15	205	6.9	5.6	0.6
Average	**0.14**	**205**	**6.9**	**5.6**	**0.6**

Bubble size distribution

The average bubble size for all conditions was within specification with the exception of control 1 (C) where the >500 μm which averaged at one oversized bubble. Results are summarised here in Table 6 and are also shown graphically in Figures 4 to 7.

Table 6. Table to summarise the bubble size distribution of microfoam generated

	Bubble Diameters (μm)			
	<30	30-280	281-500	>500
Specification	**<=20%**	**>=80%**	**<=5%**	**None**
100% CO_2, 1.2 Bar, 20 μm mesh				
Canister A1	8.2%	89.5%	2.3%	0
Canister A2	8.1%	89.7%	2.2%	0
Canister A3	7.9%	85.3%	6.8%	0
Canister A4	9.0%	88.3%	2.6%	1
Canister A5	7.9%	90.7%	1.5%	0
Canister A6	11.0%	88.1%	0.9%	0
Average	**8.7%**	**88.6%**	**2.7%**	**0**
100% CO_2, 1.2 Bar, 5 μm mesh				
Canister B1	7.8%	91.8%	0.4%	0
Canister B2	5.5%	94.2%	0.3%	0
Canister B3	8.6%	90.7%	0.7%	0
Canister B4	8.8%	91.1%	0.2%	0
Canister B5	7.7%	92.2%	0.0%	0
Canister B6	8.2%	91.3%	0.5%	0
Average	**7.8%**	**91.9%**	**0.4%**	**0**
75% CO_2/25% N_2, 0.5 Bar, 20 μm mesh				
Canister C1	8.9%	87.2%	3.9%	0
Canister C2	10.0%	89.3%	0.6%	0
Canister C3	8.9%	86.5%	4.5%	1
Canister C4	9.7%	87.7%	2.5%	4
Canister C5	10.7%	87.9%	1.5%	0
Canister C6	10.1%	88.0%	1.9%	0
Canister C11	9.6%	89.5%	1.0%	0
Canister C12	11.0%	87.6%	1.4%	0
Average	**9.7%**	**88.1%**	**2.5%**	**1.0**
75% CO_2/25% N_2, 0.5 Bar, 5 μm mesh				
Canister D1	7.8%	92.0%	0.2%	0
Canister D2	8.1%	91.4%	0.6%	0
Canister D3	10.9%	89.0%	0.1%	0
Canister D4	8.5%	91.2%	0.2%	0
Canister D5	8.8%	91.1%	0.1%	0
Canister D6	10.2%	89.8%	0.0%	0

Average	**9.0%**	**90.7%**	**0.2%**	**0**

Value from Control 1, canister 1 are not included in the average

Particulates (sub visible)

The collapsed foam from all canisters complied to specification for particulates, in so far as there were no more than 1,000 particles/ml ≥ 10 μm and no more than 100 particles/ml ≥ 25 μm. Those which had 100% CO_2 gas mixture gave the lowest numbers of particles overall. There were no visible particles seen in the collapsed microfoam. The results are summarised here in Table 7.

The appearance of foam from each device conformed to specification. The appearance of all canisters conformed to specification.

Table 7. Sub-visible particulates as per *in house* method MS14

Device No	Counts per ml			Counts per container (18 ml)			Result
	≥ 10 μm	≥ 10-25μm	≥25 μm	≥ 10 μm	≥ 10-25μm	≥ 25 μm	
Ref A Can 7	281.6	271.4	10.2	5,069	4,885	184	**Complies**
Ref A Can 8	235.3	227.9	7.4	4,235	4,102	133	**Complies**
Ref B Can 7	112.8	109.8	3	2,030	1,976	54	**Complies**
Ref B Can 8	123.1	116.3	6.8	2,216	2,093	122	**Complies**
Ref C Can 7	386.1	370.2	15.9	6,950	6,664	286	**Complies**
Ref C Can 8	369.5	350.6	18.9	6,651	6,311	340	**Complies**
Ref D Can 7	130.2	123.5	6.7	2,344	2,223	121	**Complies**
Ref D Can 8	152.1	141.4	10.7	2,738	2,545	193	**Complies**

Polidocanol identification, assay and related substances

No significant differences were observed between the results of the Control and Test preparations. All samples met all specifications for related substances, assay value and identity.

Analysis of the samples using the 25 m column was undertaken, but no significant peaks were observed relating to Nylon 6,6 interactions in these samples.

Example 4—Further study to assess the effect on physical properties of microfoam from changes to the mesh material in the mesh stack

The study of Example 3 was repeated using a device according to Figure 2 in which the shuttle mesh pore size was 20 microns, 11 microns and 5 microns, in

combination with changes to the gas pressure and gas composition in the canister. Bi-can assemblies were prepared for testing to the specifications of gas mix and pressure in the polidocanol canister detailed in Table 8.

Table 8. Summary of PD canister preparation for each treatment group

Sample Type	Gas Composition	Gas Pressure (bar absolute)	Mesh Pore Size (μm)
Control 1	75% CO_2/25% N_2	0.5	20
Control 2	100% CO_2	1.2	20
Test 2	100% CO_2	1.2	5
Test 3	100% CO_2	1.2	11

Results are shown graphically in Figure 8.

Various batches of the microfoam resulting from the test in which the shuttle mesh pore size was 11 microns had the following characteristics:

Bubble Diameters (micrometers)			
<=30	>30-280	>280-500	>500
9.2%	90.2%	0.6%	0.0%
11.8%	88.2%	0.0%	0.0%
10.6%	89.4%	0.0%	0.0%
10.2%	89.8%	0.0%	0.0%
10.6%	89.1%	0.3%	0.0%
10.5%	89.4%	0.1%	0.0%

Bubble Diameters (micrometers) excluding those below 30 μm

>30-130	>30-280	>280<=500	>500
59.1%	99.4%	0.6%	0.0%
71.2%	100.0%	0.0%	0.0%
75.3%	100.0%	0.0%	0.0%
67.3%	100.0%	0.0%	0.0%
66.4%	99.7%	0.3%	0.0%
73.6%	99.9%	0.1%	0.0%

Density and Half Life.

	Density (g/cm3)	Half Life (Min)
1	0.12	180 sec
	0.14	171 sec
	0.14	175 sec
	0.12	175 sec
	0.13	177 sec
	0.15	177 sec

exterior of the housing through one or more outlet orifices and a mechanism by which the chamber can be pressurized such that its contents pass to the exterior along the pathway and through one or more outlet orifices

said pathway to the exterior of the housing or the chamber including one or more elements defining one or more passages of cross sectional dimension, preferably diameter, 0.1 μm to 15 μm through which the contents of the chamber may be passed, whereby on passing through the passages the solution and gas form a microfoam of from 0.07 to 0.19 g/mL density and having a half-life of at least 2 minutes.

ABSTRACT

GENERATION OF THERAPEUTIC MICROFOAM

A method for producing a microfoam suitable for use in scleropathy of blood vessels, particularly veins comprises passing a mixture of a physiologically acceptable blood dispersible gas and an aqueous sclerosant liquid through one or more passages having at least one cross-sectional dimension of from 0.1 to 15 mm, the ratio of gas to liquid being controlled such that a microfoam is produced having a density of between 0.07 g/mL to 0.19 g/mL and a half-life of at least 2.5 minutes.

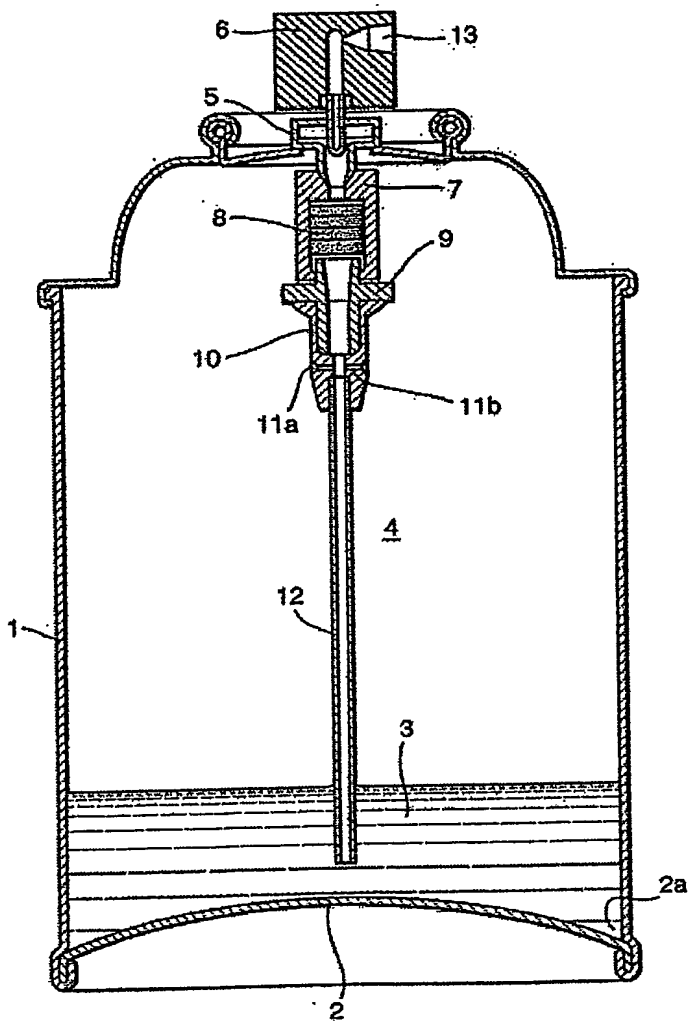

Fig. 1

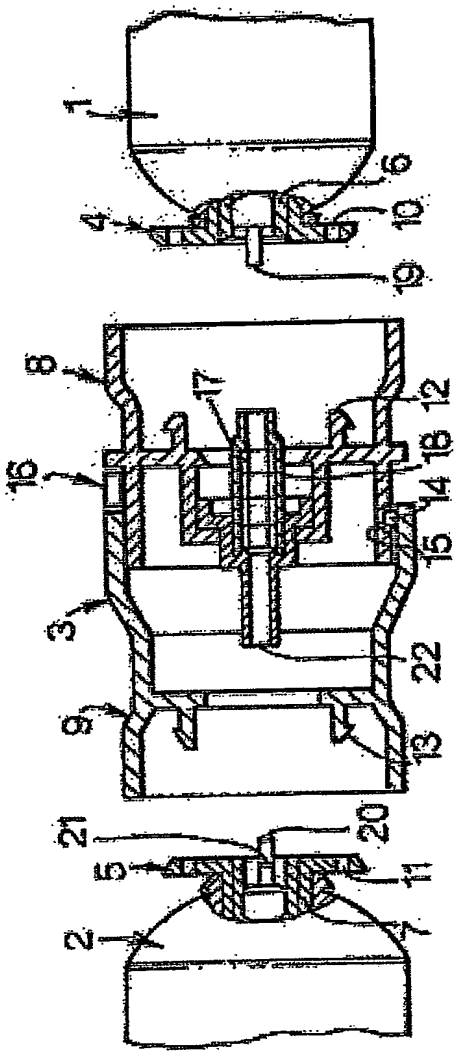

Fig. 2

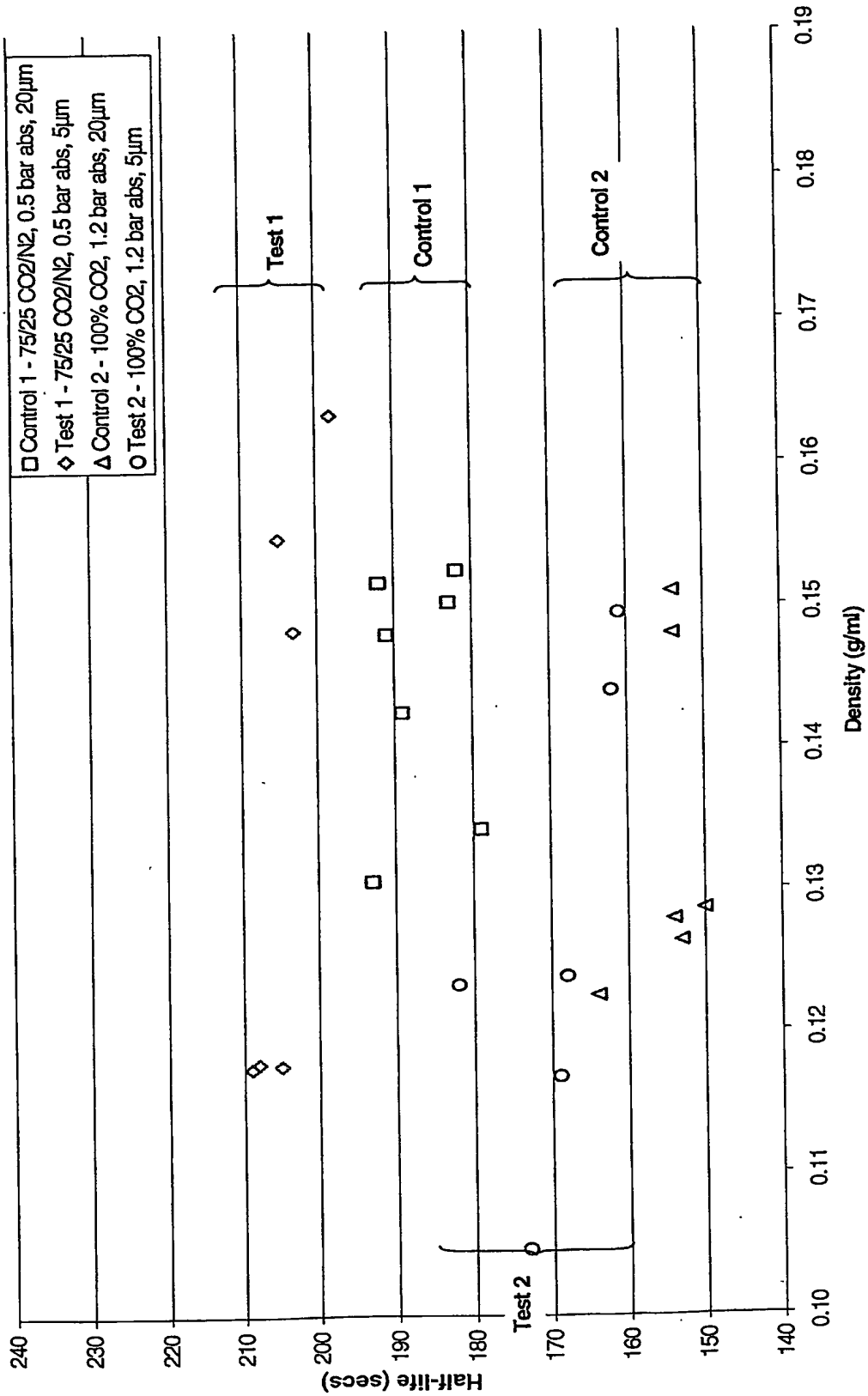
Control 1 - 75/25 CO2/N2, 0.5 bar abs, 20µm
Test 1 - 75/25 CO2/N2, 0.5 bar abs, 5µm
Control 2 - 100% CO2, 1.2 bar abs, 20µm
Test 2 - 100% CO2, 1.2 bar abs, 5µm
Test 1
Control 1
Control 2
Test 2
Half-life (secs)
Density (g/ml)
240
230
220
210
200
190
180
170
160
150
140
0.10
0.11
0.12
0.13
0.14
0.15
0.16
0.17
0.18
0.19

Fig. 3

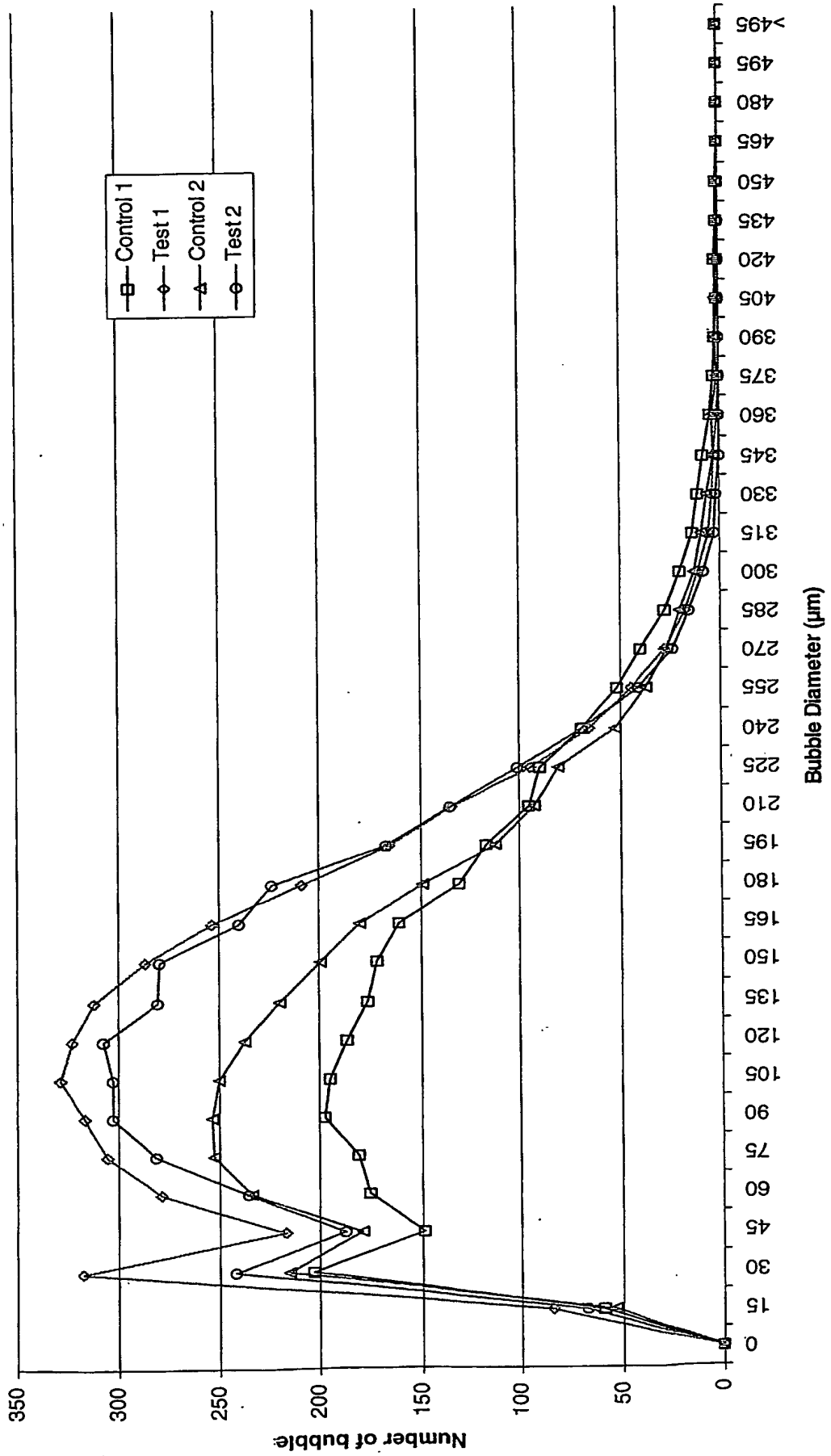
Control 1
Test 1
Control 2
Test 2
Number of bubble
350
300
250
200
150
100
50
0
Bubble Diameter (µm)
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
255
270
285
300
315
330
345
360
375
390
405
420
435
450
465
480
495
>495

Fig. 4

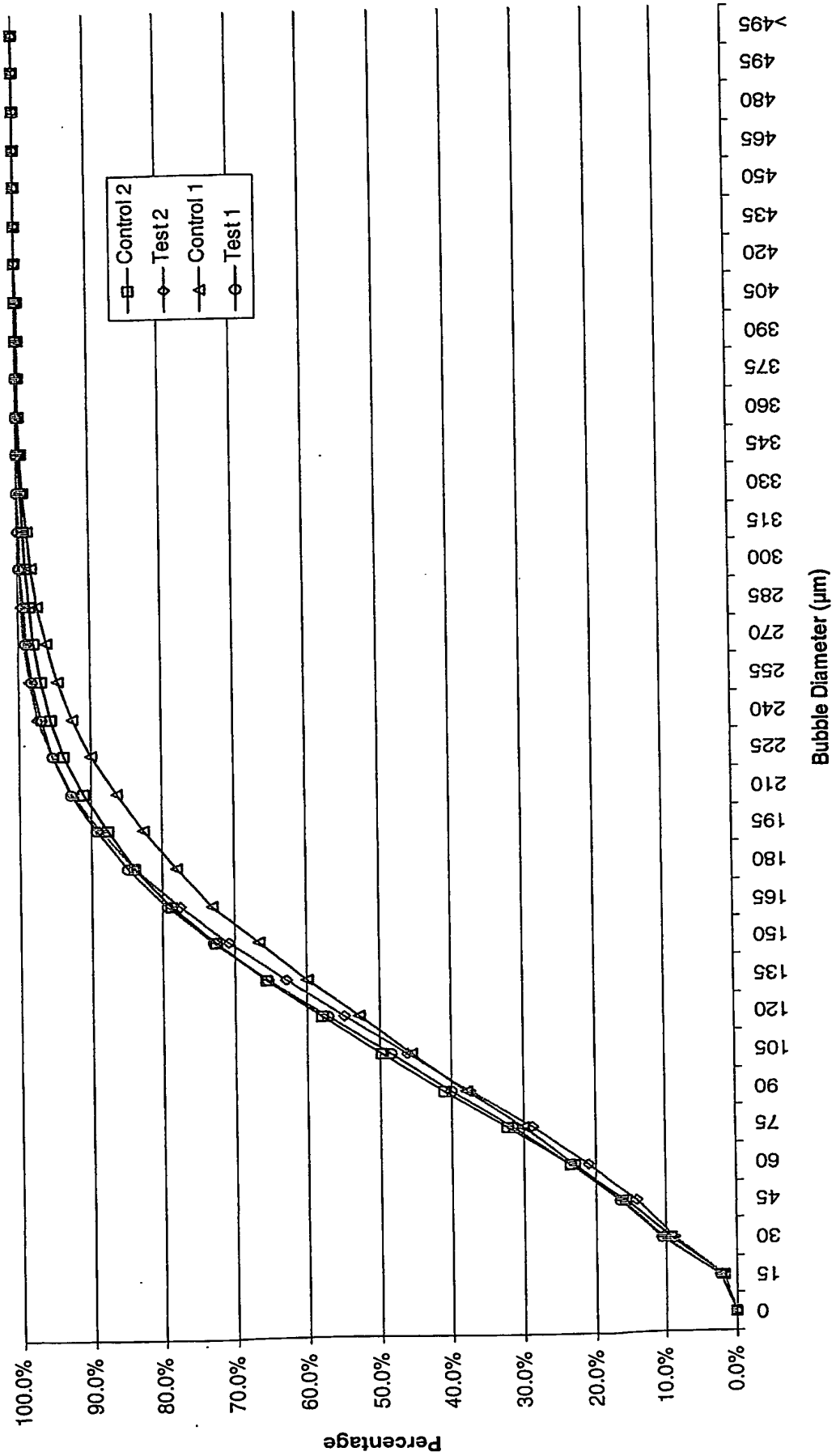
Control 2
Test 2
Control 1
Test 1
Percentage
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
Bubble Diameter (µm)
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
255
270
285
300
315
330
345
360
375
390
405
420
435
450
465
480
495
>495

Fig. 5

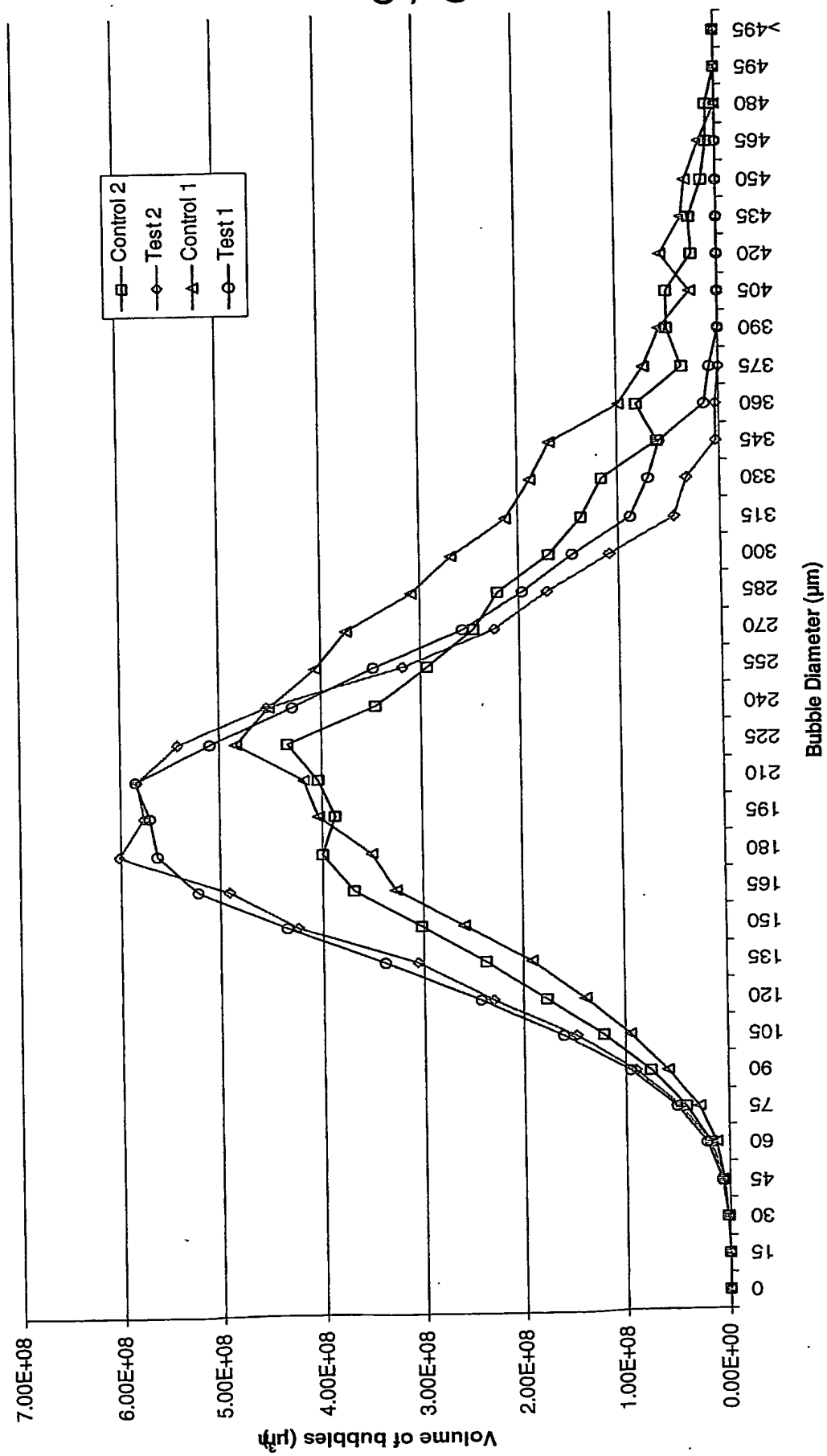
Control 2
Test 2
Control 1
Test 1
Volume of bubbles (µm³)
7.00E+08
6.00E+08
5.00E+08
4.00E+08
3.00E+08
2.00E+08
1.00E+08
0.00E+00
Bubble Diameter (µm)
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
255
270
285
300
315
330
345
360
375
390
405
420
435
450
465
480
495
>495

Fig. 6

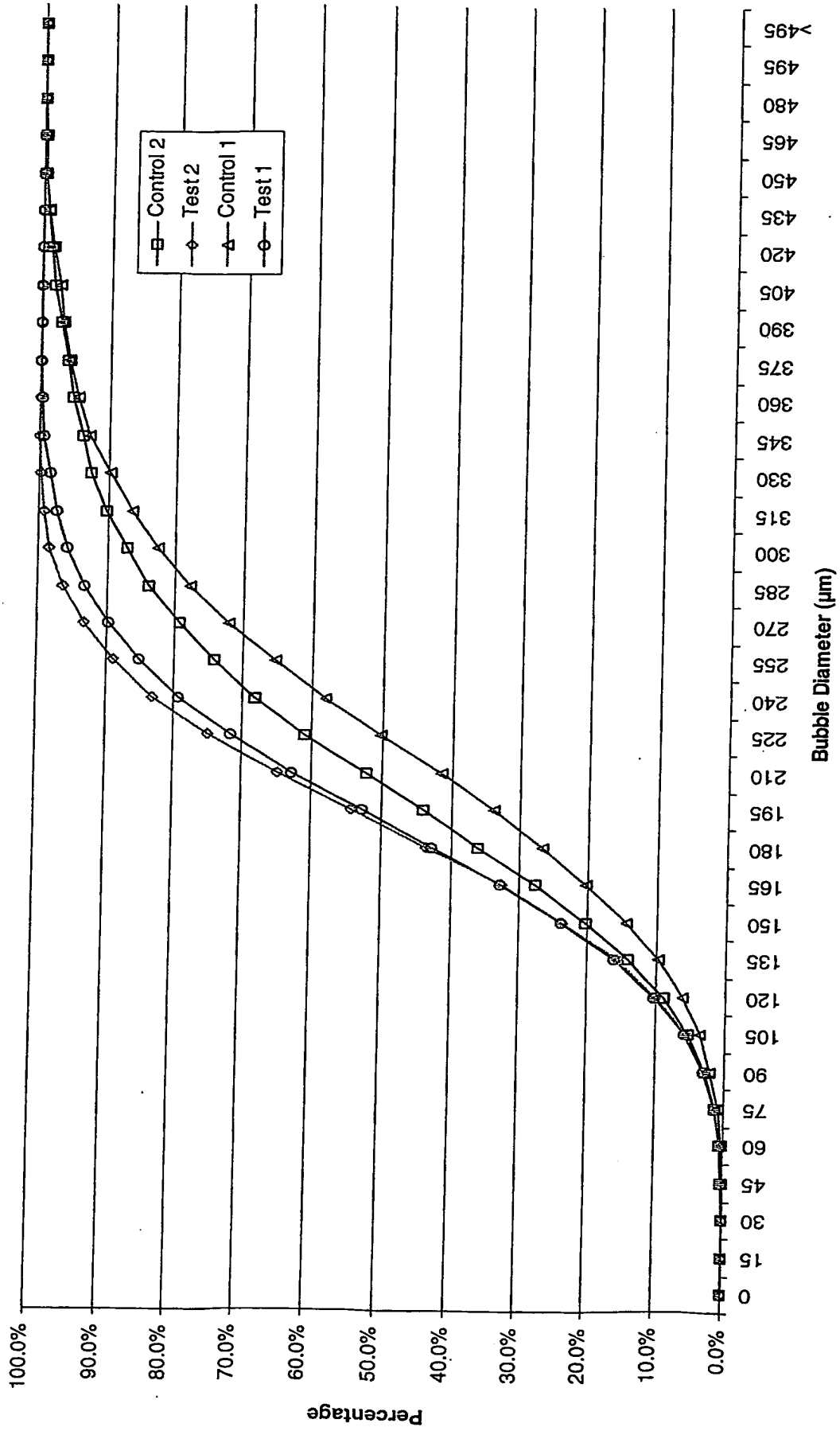
Control 2
Test 2
Control 1
Test 1
Percentage
100.0%
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
Bubble Diameter (µm)
0
15
30
45
60
75
90
105
120
135
150
165
180
195
210
225
240
255
270
285
300
315
330
345
360
375
390
405
420
435
450
465
480
495
>495

Fig. 7

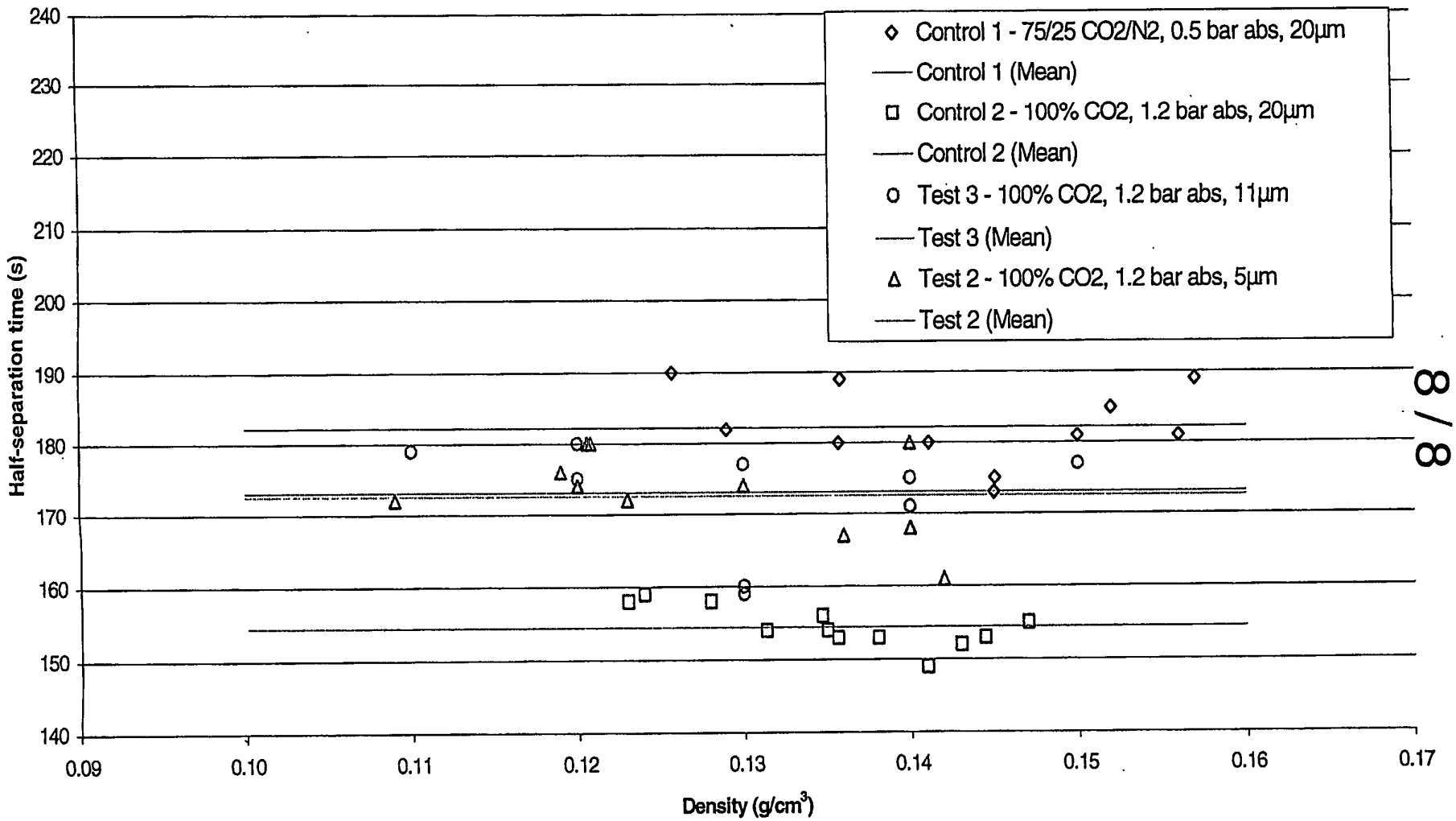
Control 1 - 75/25 CO2/N2, 0.5 bar abs, 20µm
Control 1 (Mean)
Control 2 - 100% CO2, 1.2 bar abs, 20µm
Control 2 (Mean)
Test 3 - 100% CO2, 1.2 bar abs, 11µm
Test 3 (Mean)
Test 2 - 100% CO2, 1.2 bar abs, 5µm
Test 2 (Mean)
Half-separation time (s)
240
230
220
210
200
190
180
170
160
150
140
0.09
0.10
0.11
0.12
0.13
0.14
0.15
0.16
0.17
Density (g/cm3)

Fig. 8